SEQUENTIAL SEARCH OF AN OPTIMAL DOSAGE: SOME PRELIMINARY RESULTS AND SUGGESTED AREAS FOR FURTHER RESEARCH:

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13. ABSTRACT

Sequential search procedures are described for determining an optimal dosage in the following biomedical problem. People are subjected to a certain chemotheraputic treatment and on the one hand it is desirable to give each individual the maximal possible dosage. On the other hand, high doses create undesirable toxicity, and it is undesirable to cross a certain limit of allowable toxicity level. The optimal dosage is defined as the maximal dose for which the proportion of patients in the population whose toxicity level will not cross the allowable limit is γ. In the present paper we discuss Bayesian and non-Bayesian sequential procedures for the optimal dosage, assuming a linear regression between toxicity and dosage, and normal conditional distribution of the toxicity level at each dose, with a known variance. In the two models under consideration we assume

(i) the variance at dose x is proportional to $(x-x_0)^2$ for $x > x_0$ and is zero for $x \leq x_0$;

(ii) the variance does not depend on the dose.

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Sequential Search of an Optimal Dosage: Some Preliminary Results and Suggested Areas for Further Research. †)

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1. Introduction.

The present paper summarizes our preliminary results in the area of sequential search for an optimal dosage, and brings forth several suggestions for further research. The search procedures suggested here are based on two statistical models which are specified in the next section. These models seem plausible to us. However, it may be of great interest to investigate how sensitive are the procedures to the assumptions of these models. Suggestions of how to proceed in this study of robustness will be given in Section 7. Similarly, we may try to change the objective function and investigate the possible implications. In Section 2 we specify the models under consideration and the objective functions. Section 3 provides a sequential search procedure for one of these models, in which the response variance is proportional to the dosage squared. Section 4 gives a sequential procedure for a model of fixed response variance. In Section 5 we present Bayesian sequential procedures for the models mentioned above. Monte Carlo demonstration is exhibited in Section 6. Section 7 is devoted to open problems and suggestions.

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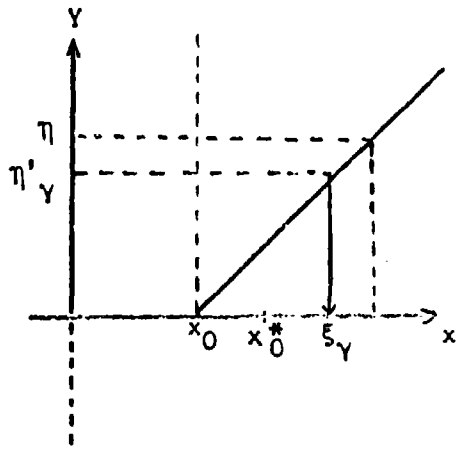
2. The Statistical Models.

Let x designate a dosage and $Y(x)$ the toxicity level at x. $Y(x)$ is a random variable. We consider here the following regression model. The toxicity level is negligible for all $0 < x \leq x_0$. From x_0 the expected value of $Y(x)$ is linear in $(x-x_0)$ with a slope b, as illustrated in Figure 1.



$$E\{Y(x)\} = b(x-x_0)$$

This assumption concerning the relationship between the expected toxicity level $E\{Y(x)\}$ and the dosage x is common to all the models specified below. The assumptions concerning the conditional distributions of $Y(x)$, given x, and how many of its parameters are known constitute the following two models:

Model 1: The conditional distribution of $Y(x)$ given x is normal with mean $b(x-x_0)$ and variance $\sigma^2(x-x_0)^2$, where σ^2 is known, and b unknown. $0 < b < \infty$.

Model 2: The conditional distribution of $Y(x)$ given x is normal with mean $b(x-x_0)$ and a known variance, σ^2; b is unknown.

As seen here, the present paper is based on the assumption that the value of σ^2 is known. Procedures of sequential search which are not based on a given value of σ^2 will be the subject of further investigations.

Let η designate the threshold of dangerous toxicity levels. It is desirable that $Y(x)$ will not exceed η. Since $Y(x)$ is a random variable we cannot guarantee with certainty that $Y(x) \leq \eta$ (unless $x \leq x_0$). We therefore require that for some tolerance probability γ, x will be such that $P\{Y(x) \leq \eta | x\} \geq \gamma$. The largest value of x for which this probability is at least γ will be designated by ξ_γ. ξ_γ will be called the optimal dose. This is the unknown parameter which we wish to find by sequential experimentation. It is easy to verify that ξ_γ is given by

$$\xi_\gamma \begin{cases} x_0 + \eta/(b+Z_\gamma\sigma), & \text{under Model 1} \\ x_0 + (\eta - Z_\gamma\sigma)/b, & \text{under Model 2,} \end{cases} \tag{2.1}$$

where $Z_\gamma = \Phi^{-1}(\gamma)$ is the γ-fractile of the standard normal distribution. The objective is to determine the dosages, x, at each stage of experimentation as close as possible to ξ_γ and not to exceed ξ_γ. Thus, the statistical problem is how to utilize the available information on the unknown parameters and determine a sequence of dosages $x_1, x_2, \ldots$, so that:

(i) For each $n = 1, 2, \ldots$

$$P_{b,\sigma}\{x_n \leq \xi_\gamma\} \geq 1 - \alpha, \text{ for all } 0 < b, \sigma < \infty. \tag{2.2}$$

Any procedure of determining $\{x_n; n \geq 1\}$ which guarantees (2.2) is called feasible.

(ii) We would further like to guarantee that $\lim_{n\to\infty} x_n = \xi_\gamma$ in probability. Such a procedure will be called consistent.

In order to secure feasibility and avoid certain theoretical difficulties we assume a knowledge of a safe dose x_0^* such that $x_0 < x_0^* < \xi_\gamma$. We can therefore restrict attention to procedures which assign dosages not smaller than x_0^*.

3. A Search Procedure for Model I.

Given the values of $x_1, \ldots, x_n$, and the associated Y values $Y_1, \ldots, Y_n$ we determine

$$\bar{U}_n = \frac{1}{n} \sum_{i=1}^{n} \frac{Y_i}{x_i - x_0} . \tag{3.1}$$

Let $\bar{U}_n^+ = \max(0, \bar{U}_n)$. The value of x_{n+1} is determined then as a function of $\bar{U}_n$ according to the formula:

$$x_{n+1} = \max\left[x_0^*, x_0 + \eta\left(\bar{U}_n^+ + \sigma\left(\frac{z_{1-\alpha}}{\sqrt{n}} + z_\gamma\right)\right)\right]; \quad n \geq 1 . \tag{3.2}$$

We prove now that this procedure is (i) feasible; (ii) consistent and (iii) optimal in a certain sense.

(i) First, consider the distribution of $U_i = Y_i/(x_i - x_0)$, $i = 1, \ldots, n$. Since x_i is a function only of $(Y_1, \ldots, Y_{i-1})$, the conditional distribution of U_i given the σ-field $\mathcal{F}_{i-1} = \mathcal{B}(Y_1, \ldots, Y_{i-1})$ is normal with expectation b and variance σ^2. Since b and σ^2 are independent of $\mathcal{F}_{i-1}$ we obtain that U_i is independent of $\mathcal{F}_{i-1}$ and has a normal distribution $\mathcal{N}(b, \sigma^2)$. Hence, $U_1, \ldots, U_n$ are i.i.d. with $\mathcal{N}(b, \sigma^2)$ distribution. This implies that

(3.3) $$P\left\{x_0 + \eta \Big/ \left(\bar{U}_n^+ + \sigma\left(\frac{Z_{1-\alpha}}{\sqrt{n}} + Z_\gamma\right)\right) \le \xi_\gamma\right\} =$$

$$P\left\{\bar{U}_n^+ + \frac{\sigma}{\sqrt{n}} Z_{1-\alpha} \ge b\right\} \ge P\left\{\bar{U}_n + \frac{\sigma}{\sqrt{n}} Z_{1-\alpha} \ge b\right\} = 1 - \alpha .$$

Let $A_n = \left\{x_0 + \eta \Big/ \left(\bar{U}_n^+ + \sigma\left(\frac{Z_{1-\alpha}}{\sqrt{n}} + Z_\gamma\right)\right) \le x_0^*\right\}$,

and let A_n^c designate the compliment of A_n. Then,

$$x_{n+1} = x_0^* \, I\{A_n\} + \left[x_0 + \eta \Big/ \left(\bar{U}_n^+ + \sigma\left(\frac{Z_{1-\alpha}}{\sqrt{n}} + Z_\gamma\right)\right)\right] I\{A_n^c\}$$

where $I\{\cdot\}$ is the indicator function. Finally, since $x_0^* < \xi_\gamma$,

$$P\left\{x_{n+1} \le \xi_\gamma\right\} \ge P\left\{x_0 + \eta \Big/ \left(\bar{U}_n^+ + \sigma\left(\frac{Z_{1-\alpha}}{\sqrt{n}} + Z_\gamma\right)\right) \ge \xi_\gamma\right\} .$$

This proves that the procedure is feasible.

(ii) By the strong law of large numbers, $\bar{U}_n \to b$ with probability one. Hence, since $b > 0$ $x_n \to \xi_\gamma$ with probability one. This proves the (strong) consistency of the procedure.

(iii) The procedure prescribed by (3.1) and (3.2) has the following optimality property:

Among all feasible procedures the procedure $\{x_n : n \ge 1\}$ prescribed by (3.1) - (3.2) is asymptotically uniformly most accurate, i.e., if $\{\hat{x}_n : n \ge 1\}$ is any sequence of dosages which satisfies the feasibility condition (2.2) then

(3.4) $P_{b,\sigma}\{\hat{x}_{n+1} < \xi'\} \ge P_{b,\sigma}\{x_{n+1} < \xi'\}$ for all (b,σ); and every $\xi' < \xi_\gamma$, and n sufficiently large (may depend on ξ').

The proof of (3.4) is based on the fact that $\bar{b}_{\alpha,n} = \bar{U}_n + \frac{\sigma}{\sqrt{n}} Z_{1-\alpha}$ is a uniformly most accurate upper confidence limit for b (see Lehmann * pp. 78-81) for each $n = 1, 2, \ldots$. Hence, if $\hat{b}_{\alpha,n}$ is any other upper confidence limit for b then

$$P_{b,\sigma}\{\hat{b}_{\alpha,n} > b'\} \geq P_{b,\sigma}\{\bar{b}_{\alpha,n} > b'\} \quad \text{for each } n = 1, 2, \ldots \tag{3.5}$$

and all (b,σ) and every $b' > b$.

Let $b^*_{\alpha,n} = \bar{U}_n + \frac{\sigma}{\sqrt{n}} Z_{1-\alpha}$ then for $n > \left(\frac{\sigma Z_{1-\alpha}}{b'}\right)^2$ we have $\{b^*_{\alpha,n} > b'\} \subset \{\bar{b}_{\alpha,n} > b'\}$. Letting $\hat{b}_{\alpha,n} = \eta/(\hat{x}_{n+1} - x_0) - \sigma Z_\gamma$ we obtain from (3.5) and (3.2) that (3.4) holds, for these values of n.

4. A Search Procedure for Model II.

Under Model II there are several complications. We still wish to estimate b by $\bar{U}_n$, as given by (3.1). However, since the sequence of x_n values is not determined before the observations commence, the sampling distribution of $\bar{U}_n$ is not normal. We cannot even apply the usual versions of the Central Limit Theorem, since $U_1, U_2, \ldots, U_n$ are dependent. It is easy to prove that $E\{\bar{U}_n\} = b$ for all (b,σ), and furthermore $\mathrm{cov}(U_i, U_j) = 0$ for all $1 \leq i < j \leq n$. Indeed, for all $i < j$,

$$E\{U_i U_j\} = E\{U_i E\{U_j / \mathcal{X}_i\}\} = b^2 . \tag{4.1}$$

Hence U_i and U_j are uncorrelated. From this result we immediately imply that

$$\mathrm{Var}\{\bar{U}_n\} = \frac{\sigma^2}{n^2} \sum_{i=1}^{n} E\left\{\frac{1}{(x_i - x_0)^2}\right\}. \tag{4.2}$$

* E.Lehman, Testing Statistical Hypotheses.

We notice in this formula that $\mathrm{Var}\{\bar{U}_n\}$ may diverge to infinity if $E\{(x_i-x_0)^{-2}\} = \infty$. In order to avoid such a possibility we require that all x_i will be greater or equal to x_0^*, where $x_0^* > x_0$. Then,

$$\mathrm{Var}\{\bar{U}_n\} \leq \frac{\sigma^2}{n(x_0^*-x_0)^2} \quad . \tag{4.3}$$

Thus we consider the following procedure: After observing $Y_1, \ldots, Y_n$ at $\hat{x}_1, \ldots, \hat{x}_n$ compute $\bar{U}_n = \frac{1}{n}\sum_{i=1}^{n} Y_i/(\hat{x}_i-x_0)$ and set

$$\hat{x}_{n+1} = \max\left(x_0^*, x_0 + (\eta-Z_\gamma\sigma)/\left(\bar{U}_n + \frac{\sigma}{\sqrt{n}}\, d_\alpha\right)\right), \tag{4.4}$$

where d_α is determined so that $\hat{x}_{n+1}$ is a feasible and consistent sequence. Employing the Chebytchev's inequality one could use, for example $d_\alpha = \alpha^{-\frac{1}{2}}(x_0^*-x_0)^{-1}$. This is however a very conservative approach. There is no doubt that more refined bounds could be determined, so that a faster convergence could be expected.

5. Bayes Procedures for Model I and Model II.

In a Bayesian framework we assume that the unknown parameter is a random variable having some prior distribution. After observing n observations $(n = 1, 2, \ldots)$ of $Y_1, \ldots, Y_n$ at dosages $x_1, \ldots, x_n$ we convert the prior distribution of b to a posterior distribution given $\mathcal{F}_n$. We then determine x_{n+1} so that the posterior probability of $\{x_{n+1} \leq \xi_\gamma\}$ given $\mathcal{F}_n$ will be at least $1 - \alpha$. This will assure that the

expectation of the left hand side of (2.2) with respect to the prior distribution of b will be at least $1 - \alpha$. This property does not imply the feasibility condition (2.2). The property that we attain is somewhat weaker and actually depends on the prior distribution assumed. We shall therefore say that a procedure is Bayes-feasible with respect to a prior distribution H of b if

$$(5.1) \qquad P_H\{x_{n+1} \leq \xi_\gamma | \mathcal{F}_n\} \geq 1 - \alpha \quad \text{for every} \quad n = 1, 2, \ldots$$

and all σ, $0 < \sigma < \infty$, $P_H\{x_{n+1} \leq \xi_\gamma | \mathcal{F}_n\}$ designates the posterior probability with respect to the distribution of b.

We provide now explicit formulae for the determination of $\{x_{n+1}, n = 1, 2, \ldots\}$ satisfying (5.1), for a normal prior distribution of b, $\mathcal{N}(\beta, V_0)$; with prior mean β and prior variance V_0. We remark here that one could use the same methodology to derive proper formulae for other prior distributions of b. Let $X_n = x_n - x_0$, $n = 1, 2, \ldots$ and as before $U_i = Y_i/X_i$, $i = 1, \ldots, n$. To give a general framework for Model I and Model II, let

$$(5.2) \qquad \tau_n^2 = \begin{cases} \sigma^2 X_n^2, & \text{under Model I} \\ \sigma^2, & \text{under Model II .} \end{cases}$$

Given $Y_1, \ldots, Y_n$ and $X_1, \ldots, X_n$, it is easy to prove that, if b has a prior normal distribution $\mathcal{N}(\beta, V_0)$ then, its posterior distribution is also normal, $\mathcal{N}(\beta_n, V_n)$, with posterior mean

$$\beta_n = \beta_{n-1} + (Y_n - \beta_{n-1}X_n)X_n V_{n-1}/(\tau_n^2 + X_n^2 V_{n-1}), \quad n = 1, 2, \ldots \tag{5.3}$$

and posterior variance

$$V_n = V_{n-1} \frac{\tau_n^2}{\tau_n^2 + X_n^2 V_{n-1}}, \quad n = 1, 2, \ldots . \tag{5.4}$$

From the recursive formulae (5.4) we obtain that the posterior variance of b is

$$V_n = \begin{cases} \dfrac{\sigma^2}{n + \sigma^2/v_0}, & \text{for Model I} \\ \sigma^2 / \left(\sum_{i=1}^{n} X_i^2 + \sigma^2/v_0 \right), & \text{for Model II} . \end{cases} \tag{5.5}$$

Thus, if all $X_i \geq X_0^*$ then V_n is in order of magnitude (in probability) of n^{-1}; i.e., $V_n = O_p(n^{-1})$ as $n \to \infty$.

Similarly we obtain that the posterior mean β_n is given explicitly, under Model I, as:

$$\beta_n = \bar{U}_n(1 + \sigma^2/nV_0)^{-1} + \beta_0(1 + \sigma^2/V_0)/(n + \sigma^2/V_0) . \tag{5.6}$$

Hence, under Model I, $\beta_n \to b$ with probability one, as $n \to \infty$. An explicit formula of β_n for Model II is considerably more complicated and we shall use the recursive formula (5.3) with $\tau_n^2 = \sigma^2$. It can be shown that β_n is a consistent estimator of b, for almost every b (with regard to H) also under Model II.

The Bayes procedure specifies the following sequence of dosages:

$$x_{n+1} = \max\{x_0^*, \hat{\xi}_{n,\gamma}\}, \quad \text{where}$$

$$\hat{\xi}_{n,\gamma} = \begin{cases} x_0 + \eta/[\beta_n + z_\gamma \sigma + z_{1-\alpha}\sqrt{V_n}\,] & , \text{ for Model I} \\ x_0 + (\eta - z_\gamma\sigma)/(\beta_n + z_{1-\alpha}\sqrt{V_n}) & , \text{ for Model II .} \end{cases} \tag{5.7}$$

6. Monte Carlo Comparisons.

In the present section we compare the various sequential procedures numerically by starting with an initial dose x_1 simulating Y_1 determining x_2 simulating Y_2 etc. We present the results of 50 such iterations. The parameters of this simulation are:

$b = 3.$, $x_0 = 0.$, $x_0^* = 1.$, $\eta = 10.$, $\sigma = 1.$, $\alpha = .05$, $\gamma = .99.$

The initial dosage is $x_1 = 3.5$. The value of ξ_γ is

$$\xi_\gamma = \begin{cases} 1.878 & , \text{ for Model I} \\ 2.558 & , \text{ for Model II .} \end{cases}$$

$\beta = 2.86$ $\qquad$ $V_0 = .25$

Table 1. Simulated Dosage Determination (x_{n+1}) for the non-Bayes (N.B.) and Bayes (B.) Procedures

	Model 1		Model 2	
n	N.B.	B.	N.B.	B.
1	1.1461	1.5678	1.0000	2.0460
2	1.2675	1.5701	1.1064	2.0513
3	1.3465	1.5737	1.2211	2.0765
4	1.4275	1.5963	1.3313	2.1221
5	1.4264	1.5778	1.3653	2.1101
6	1.4955	1.6122	1.4566	2.1652
7	1.5373	1.6328	1.5206	2.2010
8	1.5559	1.6395	1.5617	2.2171
9	1.6235	1.6847	1.6480	2.2827
10	1.6194	1.6779	1.6600	2.2787
11	1.6427	1.6928	1.6986	2.3027
12	1.6355	1.6845	1.7101	2.2955
13	1.6409	1.6863	1.7303	2.3012
14	1.6440	1.6867	1.7473	2.3047
15	1.6984	1.7296	1.8068	2.3618
16	1.6944	1.7250	1.8164	2.3580
17	1.6896	1.7199	1.8244	2.3534
18	1.7051	1.7318	1.8484	2.3702
19	1.7347	1.7560	1.8836	2.4021
20	1.7456	1.7646	1.9027	2.4142
21	1.7221	1.7438	1.8928	2.3893
22	1.7181	1.7397	1.8983	2.3854
23	1.7119	1.7336	1.9012	2.3790
24	1.7119	1.7330	1.9090	2.3793
25	1.7298	1.7481	1.9316	2.3986
26	1.7522	1.7674	1.9576	2.4227
27	1.7613	1.7751	1.9722	2.4328
28	1.7758	1.7876	1.9909	2.4485
29	1.7790	1.7902	1.9999	2.4521
30	1.7742	1.7857	2.0021	2.4478
31	1.7666	1.7786	2.0016	2.4392
32	1.7756	1.7866	2.0150	2.4493
33	1.7744	1.7852	2.0192	2.4479
34	1.7712	1.7820	2.0217	2.4447
35	1.7678	1.7787	2.0238	2.4412
36	1.7616	1.7730	2.0234	2.4356
37	1.7637	1.7745	2.0297	2.4371
38	1.7597	1.7707	2.0307	2.4331
39	1.7640	1.7744	2.0387	2.4378
40	1.7639	1.7741	2.0426	2.4377
41	1.7609	1.7712	2.0441	2.4347
42	1.7747	1.7837	2.0595	2.4493
43	1.7836	1.7917	2.0712	2.4586
44	1.7917	1.7991	2.0818	2.4675
45	1.8026	1.8091	2.0946	2.4791
46	1.8094	1.8153	2.1039	2.4864
47	1.8141	1.8196	2.1113	2.4914
48	1.8078	1.8136	2.1094	2.4845
49	1.7984	1.8048	2.1037	2.4756
50	1.8053	1.8140	2.1163	2.4835

The simulated dosage values which are exhibited in Table 1 illustrate the approach of these sequences of doses to the optimal doses, given by ξ_γ. In Model I the Bayes procedure yields dosages which are somewhat closer to the optimal. The differences between the non-Bayes and the Bayes procedures become insignificant as n grows. This phenomenon depends however on a "good" choice of prior parameters for the Bayes procedure. A similar phenomenon is observed in Model II. The non-Bayes procedure (derived in Section 4) yields at the beginning values of x close to x_0^* and the convergence is slow. This is due to the "over pessimistic" choice of the d_α parameter in (4.4). We further observe that in no case the dosages obtained exceed the optimal dose ξ_γ. This is valuable characteristic of the proposed procedures.

7. Suggestions for Further Research.

The following suggestions for further research are based on our own speculations concerning the relevancy of the models studied in the previous sections. Our list of open problems is classified into two major classes. (i) Variations of the statistical assumptions and objectives within the framework of the present problem. (ii) Extension of the models into multivariate, multi-dimensional and time dependent problems. Within the first major class we suggest to consider the following problems

(1.1) The conditional distribution of toxicity levels, $Y(x)$, for a given dosage, x, is normal with mean $b(x-x_0)$ and unknown variance $\sigma^2(x)$. This variant of the statistical model can be further broken up into several special cases.

(1.2) Problems connected with unknown intercepts (place of x_0) and known or unknown variances, assuming still normal conditional distributions.

(1.3) The effect on the procedures caused by deviations from normality of the conditional distributions around the regression lines.

(1.4) Derivation of search procedures when the toxicity can assume values only on a discrete set.

(1.5) Deviations from linearity of the toxicity-dosage regression line.

(1.6) Sensitivity analysis - study of the robustness of the search procedures concerning the basic assumptions on the distributions and on the toxicity-dosage regression.

(1.7) Formulation of different types of objective functions.

In the second class of open problems we mention:

(2.1) Multivariate response - the observations consist of vectors of several components, one of which is toxicity.

(2.2) Time dependent problems - patients are subject to continual treatment. The effect of prior treatments on future dosages, employing the information gathered on each individual separately. The determination of the optimal spacing between epochs of treatments.

(2.3) The search for the optimal combination of various drugs.